The Diels-Alder Reaction of N, N-Diethyl-1, 3-butadienylamine with Several (β-Substituted Styrenes and Use of the Reaction Products for the One-Pot Synthesis of 2-Substituted Biphenyls

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The Dield-Alder reaction of *N,N*-diethyl-1,3-butadienylamine with several β-substituted styrenes was investigated. The reaction products isolated were easily converted to the corresponding 2-substituted biphenyls, respectively, by combining the two reactions, *viz.*, oxidative deamination using *m*-chloroperbenzoic acid and dehydrogenation by $K_3Fe(CN)_6$ in the presence of KOH.

KEY WORDS: Reaction of *N,N*-diethyl-1,3-butadienylamine/ Reaction of β-substituted styrenes/ Deamination of 3-*N, N*-diethylamino-5-phenylcyclohexene derivatives/ Dehydrogenation of 5-phenyl-1,3-cyclohexadiene derivatives/ Oxidation of 4-acetyl-3-*N,N*-diethylamino-5-phenylcyclohexene/

N,N-Diethyl-1,3-butadienylamine (**1**) has been found to undergo the Diels-Alder reaction with a variety of dienophiles. Thus, fulvenes,[1] benzonitrile oxide,[2] benzofurazan oxide,[3] triafulvene,[4] dehydrobenzene,[5] *trans*-diaroylethenes,[6] alkyl esters of atropic acid,[7] acetylene carboxylic acid esters[6] and α, β-unsaturated carbonyl compounds[9] such as acrolein, alkyl acrylates and alkyl vinyl ketones each gave adducts. To our knowledge, however, none is known about the Diels-Alder reaction of **1** with β-substituted styrenes (**2**) in which the substituent is a electron-withdrawing group, although some of them may be classified into the so-called α, β-unsaturated carbonyl compounds. In this paper, we describe experiments which show that the reaction of **1** with **2** gave a useful precursor for the preparation of 2-substituted biphenyls (**7**).

First, we studied the Diels-Alder reaction of **1** with methyl styryl ketone (**2a**) and found that the reaction proceeded smoothly to afford 4-acetyl-3-*N,N*-diethylamino-5-phenylcyclohexene (**3a**) in a fairly good yield. The reaction was extended to methyl cinnamate (**2b**), cinnamonitrile (**2c**), phenyl styryl ketone (**2d**), phenyl cinnamate (**2e**), and β-nitrostyene (**2f**) with the results summarized in Table I.

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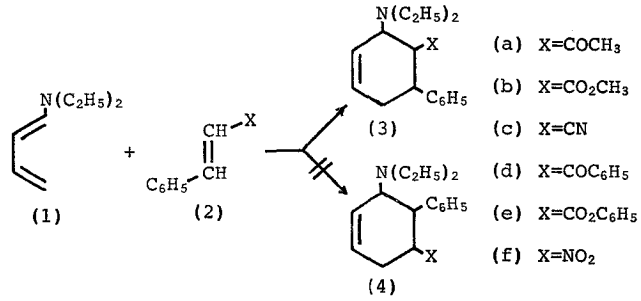


Table I. The Diels-Alder Reaction of *N,N*-Diethyl-1,3-butadienylamine (**1**) with Various *β*-Substituted Styrenes (**2**)

Run	2 used (Mole ratio, 2/1)	Reaction conditions solvent/tempearture/time	Product[a]	Yield (%)[b]	Found (Calcd) (%) C	H	N	MS (40 eV) *m/e* (M^+)
1	**2a** (0.70)	Toluene/reflux/30 h	**3a**	64	79.91 (79.66)	9.45 (9.29)	5.35 (5.16)	271
2	**2b** (0.35)	Neat/140–150°C/10 h	**3b**	50	75.45 (75.22)	8.80 (8.77)	4.57 (4.87)	287
3	**2c** (0.35)	Neat/140–150°C/10 h	**3c**	71	80.25 (80.27)	8.97 (8.72)	10.76 (11.01)	254
4	**2d** (0.70)	Toluene/reflux/30 h	**3d**	92	82.58 (82.84)	8.36 (8.16)	4.45 (4.20)	333
5	**2e** (0.70)	Toluene/reflux/30 h	**3e**	85	79.19 (79.05)	7.68 (7.79)	4.22 (4.01)	349
6	**2f** (0.70)	Ether/25°C/2 h	**3f**	78	70.37 (70.04)	7.92 (8.08)	10.07 (10.21)	274

a) The ^{1}H-NMR spectra (60 MHz, δ, in $CDCl_3$) are as follows: **3a**: 0.96 (t,6H), 1.72 (s,3H), 2.0–2.8(m,5H), 2.8–3.2(m,3H), 3.6–3.9(m,1H), 5.7–5.9(m,2H), 7.0–7.2(m,5H). **3b**: 1.02(t,6H), 2.1–3.6(m,8H), 3.32(s,3H), 3.8–4.0(m,1H), 5.8–6.0(m,2H), 7.1–7.2(m,5H). **3c**: 1.12(t,6H), 2.0–3.1(m,8H), 3.5–3.9(m,1H), 5.6–5.9(m,2H), 7.1–7.4(m,5H). **3d**: 0.79 (t,6H), 2.1–2.8(m,6H), 3.0–3.5(m,1H), 3.7–4.1(m,2H), 5.8–6.0(m,2H), 6.8–7.8(m,10H). **3e**: 1.08(t,6H), 2.1–3.5(m,8H), 3.7–4.1(m,1H), 5.8–6.0(m,2H), 6.9–7.4(m,10H). **3f**: 0.93(t,6H), 2.0–2.8(m,6H), 3.0 3.6(m,1H), 3.6–4.2(m,1H), 4.5–5.1(m,1H), 5.5–5.7(m,1H) 6.9–7.1(m,5H). b) Yield was based upon **2**, and was of the isolated product.

On the other hand, analysis of the above reaction mixtures failed to indicate the presence of any products resembling **4**. These observation suggest that the cycloaddition exclusively proceeds in such direction that both components with a partial charge-polarization attract each other.

The conversion of **3** into the corresponding 5-phenyl-1,3-cyclohexadiene derivatives (**6**) may easily be accomplished using H_2O_2 in boiling methanol or *m*-chloroperbenzoic acid (MCPBA) in boiling benzene. To explain the formation of **6** we must assume the formation of the intermediate *N*-oxides (**5**) which are split under the reaction conditions to yield **6** and *N,N*-diethylhydroxylamine (the Cope reaction). The results obtained by the oxidative deamination of **3** with H_2O_2 or with MCPBA are listed in Table II, along with the analytical data of the products.

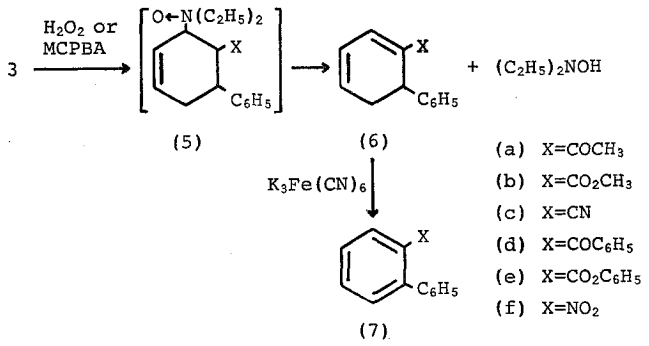


Table II. Oxidative Deamination of 3-(*N,N*-Diethylamino)-5-phenylcyclohexene Derivatives (**3**) to 5-Phenyl81,3-cyclohexadiene Derivatives (**6**)

Run	3 used	Oxidizing agent/solvent	Product[a]	Yield[b]	Found (Calcd) (%)			MS (40 eV) *m/e* (M^+)
					C	H	N	
1	**3a**	H_2O_2/methanol	**6a**	84	84.57 (84.81)	7.01 (7.12)		198
2	**3b**	H_2O_2/methanol	**6b**	46	78.23 (78.48)	6.74 (6.59)		214
3	**3c**	MCPBA[c]/benzene	**6c**	13	85.89 (86.16)	6.01 (6.12)	7.97 (7.73)	181
4	**3d**	H_2O_2/methanol	**6d**	36	87.54 (87.66)	6.35 (6.19)		260
5	**3e**	H_2O_2/methanol	**6e**	37	82.57 (82.58)	6.09 (5.84)		276
6	**3f**	MCPBA[c]/benzene	**6f**	29	71.77 (71.62)	5.56 (5.51)	6.78 (6.96)	201

a) The ^{1}H-NMR spectra (60 MHz, δ, in $CDCl_3$) are as follows: **6a**: 2.18(s,3H), 2.60 (dd,1H), 5.6–6.2(m,2H), 6.8–7.2(m,6H). **6b**: 2.5–2.9(m,2H), 3.62(s,3H), 4.04(dd,1H), 5.9–6.4(m,2H), 7.1–7.5(m,6H). **6c**: 2.5–2.8(m,2H), 3.4–3.9(m,1H), 5.9–6.1(m,2H), 6.6–6.8(m,1H), 7.1–7.3(m,5H). **6d**: 2.78(dd,2H), 4.30(dd,1H), 6.0–6.2(m,2H), 7.0–7.8(m, 11H). **6e**: 2.78(dd,2H), 4.06(dd,1H), 5.9–6.2(m,2H), 6.7–7.5(m,11H). **6f**: 2.7–3.1(m, 2H), 4.30(dd,1H), 6.0–6.2(m,2H), 7.1–7.2(m,5H), 7.4–7.6(m,1H). b) Yield was based upon **3**, and was of the isolated product. c) *m*-Chloroperbenzoic acid.

In order to establish the conversion of **3** into **7** in one pot, **3** was subjected to the above oxidative deamination by MCPBA and successively to a dehydrogenation reaction by $K_3Fe(CN)_6$ in the presence of KOH, without isolation of the intermediate **6**. The dehydrogenation reaction was effected only under basic reaction conditions using $K_3Fe(CN)_6$ as oxidizing agent. The other oxidizing agents such as sulfur, Pd on carbon, Se, several quinones etc., don't catalyze the dehydrogenation reaction. The results obtained in the above combined sequence are summarized in Table III. Thus, the method here described constituted a facile and convenient synthesis of **7** from **2**.

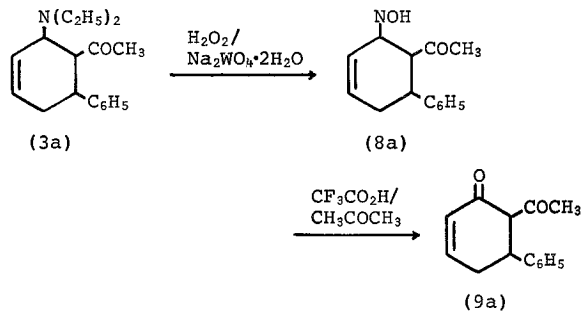
When **3a** was oxidized under conditions similar to those used by Zimmerman and co-workers[10] for conversion of 2-*N,N*-dimethylamino-*trans*-5,6-diphenylbicyclo [3.1.0]hexane to *trans*-5,6-diphenylbicyclo-[3.1.0]hexan-2-one, the formation of the

Table III. Conversion of 3-(*N,N*-Diethylamino)-5-phenylcyclohexene Derivatives (**3**) to Biphenyl Derivatives (**7**) by Oxidative Deamination Followed by Dehydrogenation

Run	3 used	Product	Yield (%)[a]	Found (Calcd) (%)			MS (40 eV) *m/e* (M^+)	^{1}H-NMR spectra (60 MHz, δ, in $CDCl_3$)
				C	H	N		
1	**3a**	**7a**	37	85.91 (85.68)	6.10 (6.16)		196	1.98 (s, 3H), 7.1–7.6 (m, 9H)
2	**3b**	**7b**	25	79.37 (79.22)	5.76 (5.70)		212	3.58 (s, 3H), 7.0–7.2 (m, 9H)
3	**3c**	**7c**	10	87.01 (87.12)	5.22 (5.06)	7.75 (7.82)	179	7.1–8.0 (m, 9H)
4	**3d**	**7d**	15	88.01 (88.34)	5.74 (5.46)		258	7.2–8.2 (m, 14H)
5	**3e**	**7e**	17	82.98 (83.20)	5.31 (5.15)		274	7.0–7.8 (m, 14H)
6	**3f**	**7f**	28	72.44 (72.35)	4.37 (4.55)	6.89 (7.03)	199	7.2–8.4 (m, 9H)

a) Yield was based upon **3**, and was of the isolated product.

corresponding ketone, 6-acetyl-5-phenylcyclohex-2-en-1-one (**9a**), was not recognized, but 6-acetyl-5-phenylcyclohex-2-en-1-one oxime (**8a**) was isolated in moderate yield. Similarly, 4-benzoyl-3-*N,N*-diethylamino-5-phenylcyclohexene (**3d**) was converted into 6-benzoyl-5-phenylcyclohex-2-en-1-one oxime (**8d**), but the yield was much lower. On the other hand, when the other 3-*N,N*-diethylamino-5-phenylcyclohexene derivatives (**3b, 3c, 3e,** and **3f**) were submitted to this conversion, none of the corresponding oxime was isolated, indicating that the oxidation procedure lacks generality although it is a unique method for the preparation of **8a**. Treatment of **8a** in acetone with trifluoroacetic acid at room temperature produced 6-acetyl-5-phenylcyclohex-2-en-1-one (**9a**) in almost quantitative yield.



(3a) (8a) (9a)

EXPERIMENTAL

The Diels-Alder Reaction of *N,N*-Diethyl-1,3-butadienylamine (1) With β-Substituted Styrene (2). Eight mmol (1.0 g) of **1**, a β-substituted styrene (**2**) and 20 ml of toluene or ether as solvent were mixed at room temperature (the mole ratio of **2** to **1** and the solvents used for the reaction are listed in Table I, but the solvent was omitted in Runs 2 and 3). The reaction mixture was heated under a

nitrogen atmosphere in the manner described in Table I, and poured into 50 ml of 5% HCl. After being stirred thoroughly, the aqueous layer was separated, and the organic layer was extracted with 50 ml of 5% HCl. The combined acid fraction was washed with ether, basified with excess of aqueous Na_2CO_3 and extracted repeatedly with ether. The combined ethereal extract was dried, and the volatile solvent was removed under reduced pressure leaving a brown residue, which was chromatographed (Al_2O_3, 10% chloroform-hexane).

Synthesis of 5-Phenyl-1,3-cyclohexadiene Derivatives (6). All of **6** listed in Table II were obtained by either of two procedures, *i.e.* oxidative deamination by H_2O_2 in methanol and that by *m*-chloroperbenzoic acid in benzene. The former was adopted in the reaction using **3a**, **3b**, **3d**, and **3e** as the starting substrate and the latter in the reaction using **3c** and **3f** as the starting substrate. Hence, only one example of each will be described in detail.

Synthesis of 4-Acetyl-5-phenyl-1,3-cyclohexadiene (6a). To a solution of 0.33 g (1.2 mmol) of **3a** in 15 ml of methanol, 1.1 g (9.7 mmol) of a 30% solution of H_2O_2 in water was added. The reaction mixture was heated under reflux for 5 h. After cooling, 0.2 g (2.3 mmol) of MnO_2 was added, after which the stirring was continued for 1 h at room temperature. The precipitate was then filtered off with suction and washed thoroughly with a small amount of methanol. The combined filtrate and washings was added to 50 ml of water and extracted repeatedly with ether. The combined ethereal extracts were dried, and the volatile solvent was removed under reduced pressure leaving a residue, which was chromatographed (SiO_2, 10% chloroform-hexane).

Synthesis of 4-Cyano-5-phenyl-1,3-cyclohexadiene (6c). To a solution of 0.30 g (1.4 mmol) of MCPBA (80%) in 10 ml of benzene, 0.27 g (1.1 mmol) of **3c** was added. The reaction mixture was heated under reflux for 5 h. After cooling, 0.2 g (2.3 mmol) of MnO_2 was added, after which the stirring was continued for 1 h at room temperature. The reaction mixture was filtered, and the precipitate was washed thoroughly with a small amount of benzene. The combined filtrate and washings was added to 10 ml of aqueous $NaHCO_3$. After being stirred thoroughly the benzene layer was separated, dried, and the volatile solvent was removed under reduced pressure leaving a residue, which was chromatographed (SiO_2 10% chloroform-hexane).

Synthesis of 2-Substituted Biphenyls (7) from 3-*N*, *N*-Diethylamino-5-phenylcyclohexene Deruvatives (3). All of **7** were prepared in a similar manner and hence only the preparation of 2-acetylbiphenyl (**7a**) will be described. To a solution of 0.30 g (1.4 mmol) of MCPBA (80%) in 10 ml of benzene, 0.30 g (1.1 mmol) of **3a** was added. The reaction mixture was heated similarly as above. After cooling, 0.9 g (2.7 mmol) of $K_3Fe(CN)_6$ in 10 ml of water and 0.5 g (8.9 mmol) of KOH in 5 ml of methanol were added successively, and the mixture was heated under reflux for 10 h and then poured into 30 ml of water. The organic layer was separated, combined with an ethereal extract of the aqueous phase, dried, and the

volatile solvent was removed under reduced pressure leaving a residue, which was chromatographed (SiO_2, 20% benzene-hexane).

Synthesis of 6-Acetyl-5-phenylcyclohex-2-en-1-one Oxime (8a). To a solution of 0.50 g (1.8 mmol) of **3a** and 1.0 g (3.0 mmol) of $Na_2WO_4 \cdot 2H_2O$ in 15 ml of methanol, 1.1 g (9.7 mmol) of a 30% solution of H_2O_2 in water was added with stirring at 0°C. The mixture was heated under reflux for 5 h. After reaction, it was poured into 40 ml of aqueous $NaHSO_3$ and extracted with several portions of ether. The combined ethereal extracts were dried, filtered, and concentrated *in vacuo* to give a residue, which was recrystallized from hexane to provide **6a**. Yield 0.31 g (73%). Anal. Found: C,73.61; H,6.64; N,6.02%. Calcd for $C_{14}H_{15}NO_2$: C,73.34; H,6.59; N,6.11%. MS (40 eV): m/e=229 (M^+). ^{1}H-NMR spectra (60 MHz, δ, in $CDCl_3$): 1.12(s,3H), 2.60(dd,2H), 2.8–3.0(m,1H), 3.0–3.4(m,2H), 6.2–6.4(m,2H), 7.0–7.2(m,5H).

Synthesis of 6-Benzoyl-5-phenylcyclohex-2-en-1-one Oxime (8d). This compound was prepared by the same procedure that was used for the preparation of **8a** from **3a**, starting from 0.6 g (1.8 mmol) of **3d**. Yield 0.068 g (13%). Anal. Found: C,78.12; H,5.62; N,4.87%. Calcd for $C_{19}H_{17}NO_2$: C,78.33; H,5.88; N, 4.81%. MS (40 eV): m/e=291 (M^+). ^{1}H-NMR spectra (60 MHz, δ, in $CDCl_3$): 2.1–2.6(m,2H), 3.2–3.6(m,2H), 3.6–3.9(m,1H), 6.2–6.5(m,10H).

Synthesis of 6-Acetyl-5-phenylcyclohex-2-en-1-one (9a). To a solution of 0.070 g (0.31 mmol) of **8a** in 20 ml of acetone, 0.44 g (3.9 mmol) of trifluoroacetic acid was added. The mixture was stirred at room temperature for 2 h. After reaction, it was poured into 20 ml of aqueous $NaHCO_3$ and extracted with several portions of ether. The combined ethereal extracts were dried, filtered, and concentrated *in vacuo* to give a residue, which was chromatographed (SiO_2, 10% chloroform-hexane). Yield 0.063 g (96%). Anal. Found: C,78.30; H,6.59%. Calcd for $C_{14}H_{14}O_2$: C,78.48; H,6.59%. MS (40 eV): m/e=214 (M^+). ^{1}H-NMR spectra (60 MHz, δ, in $CDCl_3$): 1.82 (s,3H), 2.3–2.8 (m,2H), 4.00(t,1H), 6.1–6.4(m,1H), 7.1–7.2(m,5H).

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